Section II (Remarks)

A. Summary of Amendments to the Claims

By the present Amendment, claims 3, 4, 21 and 22 are cancelled, and claims 1 and 18 are amended. Claims 10-17 have been withdrawn. New claims 23-28 have been added.

The amendments made herein are fully consistent with and supported by the originally filed disclosure of this application. Specifically, support for the amendments to claim 1 and claims 18 and 23-28 is found at page 2, paragraph 25, at page 3, paragraph 26, and at pages 4 and 5, paragraphs 64 – 71, of the published patent application. Additional support is found in Figures 6 and 13.

No new matter (35 U.S.C. 132) has been introduced by the foregoing amendments.

B. Rejection of Claims Under 35 U.S.C. 112, Second Paragraph

In the September 27, 2007 Office Action, claims 1-9 and 18-22 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Specifically, the Office Action contends that the applicants' use of the term "protein transduction domain" in claim 1 is vague and indefinite. (Office Action, pg. 3, ll. 7-9) Applicants respectfully disagree, and traverse such rejection as applied to amended claim 1, in view of the following remarks.

The examiner's attention is respectfully directed to the following relevant section of the MPEP,

> "[T]he ordinary and customary meaning of a claim term is the **meaning that the term would have to a person of ordinary skill in the art** in question at the time of the invention..." *Phillips v. AWH Corp.*, *>415 F.3d 1303, 1313<, 75 USPQ2d 1321>, 1326< (Fed. Cir. 2005) (en banc). MPEP 2111.01 (Plain Meaning) (emphasis added).

As indicated by the above relevant section of MPEP 2111.01, the ordinary and customary meaning of a claim term is the meaning that a term would have to a person of ordinary skill in the art. A "protein transduction domain" or "PTD" is a well known term to those skilled in the art, having the following generally accepted meaning. A protein transduction domain is a permeable peptide capable of translocating drugs or drug-containing particles into cellular cytoplasm or

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nucleus. It is able to introduce oligonucleotides, peptides, proteins, oligosaccharides, polysaccharides and nanoparticles into cell without receptors, transporters and energy. As support, the Applicants refer the examiner to paragraph 1 and 2 at page 1570 of Exhibit A, which describes a PTD.

In other words, PTD is a technical term that implies all peptides capable of introducing materials such as peptide into cells without receptors, transporters and energy, and it is well-known to ones skilled in the art that PTD includes TAT, drosophila melano gaster-derived Antp peptide, VP22 peptide, mph-1-btm and TAT-mutants (Yohei Mukai et al., Biol. Pharm. Bull., 29(8):1570, 2006: the reference 1). Therefore, those skilled in the art can choose one among the known PTDs and use it in order to carry out the present invention.

In addition, the attached NCBI searching results (the reference 2) also demonstrate that PTD is a well-known term to one skilled in the art. Also, it is clear that PTD is a commonly used term, from the following search results:

(a) In case of searching for PTD and "protein transduction domain": 104 results

(b) In case of searching for PTD: 707 results

(c) In case of searching for "protein transduction domain": 231 results

Based on the foregoing, the term "protein transduction domain" and its abbreviation "PTD" are submitted to be fully known and understood in the art, with respect to their meaning.

Concerning the rejection of claims 1, 3 and 4, claim 1 has been amended herein and claims 3 and 4 cancelled.

Concerning claim 21, and the rejection thereof under 35 U.S.C. 112, second paragraph, claim 21 has been amended to recite "a composition for the treatment of fibrosis or cirrhosis of organs," as suggested by the examiner.

Concerning the rejections of claims 2, 5-9, 18-20 and 22, it is submitted that such claims, by virtue of their dependence under claim 1, also overcome the rejection.

C. Rejections Under 35 U.S.C. 103(a)

It is elemental law that in order for an invention to be obvious, the difference between the subject matter of the application and the prior art must be such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art.

In order to meet this standard for a proper §103 rejection, **all claim limitations must be disclosed in or derivable from the cited combination of references**, there must be a logical reason to combine the cited references to produce an operable combination and there must be a reasonable expectation of success. (emphasis added) See MPEP §2143:

> **"2143 Basic Requirements of a Prima Facie Case of Obviousness**
>
> "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, **the prior art reference** (or references when combined) **must teach or suggest all the claim limitations."**
>
> "The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

To support a rejection under 35 U.S.C. 103, the prior art reference(s) must disclose or provide a basis for all of the limitations of the claims. MPEP § 2143.03.

Concerning the rejection of claims under 35 U.S.C.(a) over Herr, which is traversed by applicants, the examiner has stated that the '867 publication, as described on pages 12-13 of the specification of the present application, discloses fusion polypeptides comprising an osteoinductive polypeptide and PTD.

The examiner has contended that the presence of FAD is the only difference between the present invention and the disclosure of the '867 publication. This is incorrect, and ignores the following aspects of applicants' claimed invention.

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The commercially available conventional hBMPs have problems in that they have to maintain their 3-dimensional structure from the production step to the administration in order to keep up their activities. Therefore, the object of present invention is to solve the problems such as complicated separation and purification steps of hBMP, difficulties in storage for maintaining its 3 dimensional structure and inefficiency upon administration due to its 3 dimensional structure. In the case where hBMP combines with only PTD, the same problem occurs, but by fusing hBMP with FAD and PTD, it is no longer necessary to maintain 3-dimensional structure of hBMP, which is a new breakthrough development presented by the present inventors for the first time.

The present application discloses on pages 25-28 in Example 1 an experimental result obtained by preparing PTD-hBMP with the removal of 2-and 3-dimensional structures of BMP, in which PTD-hBMP with the removal of 3-dimensional structure permeated cells, but did not show biological activity, contrary to commercially available rhBMP-2 maintaining 2-dimensional structure.

Meanwhile, the '867 publication merely suggests fusion polypeptides comprising PTD; and LMP and other various downstream genes (BMP-2, BMP-4, BMP-6, BMP-7, TGF-beta 1 and SMAD; Summary of Invention [0014, 0015]). It also suggests BMP, TGF-beta and SMAD as osteoinductive polypeptide capable of replacing LMP-1, but it does not show actual experimental data obtained from and experiment carried out by binding PTD to BMP.

The disclosure of the '867 publication is based on the experimental results and references showing that bond formation was also induced when the expression of LMP was induced. LMP is an intracellular protein unlike BMPs and TGF-beta. LMP is a protein found in the osteogenic differentiation induction process (Bodon S.D. et al., Endocrinol., 139:5125, 1998). LMP proteins consist of LIM domain (Liu Y. et al., J. Bone Miner. Res., 17:406, 2002) and PDZ domain (Vallenius T. et al., J. Biol. Chem., 275:11100, 2000) conserved in the LMP-1, LMP-2 and MLM-3. These domains are known as a protein interaction motif (Fanning A.S. & Anderson J.M., J. Clin. Invest., 103:767, 1999). In fact, it was known that PDZ-LIM protein family plays a

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role of an adaptor between intracellular cytoskeleton and kinase (Guy P.M. et al., Mol. Cell Biol., 10:1973, 1999; Zhou Q. et al., J. Biol. Chem. 274:19807, 1999).

The '867 publication asserts that bone formation will be induced when combining LMP, which is PDZ-LIM protein, with PTD (protein transduction domain) and then administering the recombinant, based on their suggestion that the expression of intracellular mRNA is increased and the level of intracellular BMP-2 and BMP-7 proteins is increased when LMP-1 is overexpressed on the culture cells by using adenovirus ('867 publication, FIG. 2). In addition, Smad-1, Smad-2, Smad-3, Smad-4, Smad-5, Smad-6, Smad-7 and Smad-8, which are Smad proteins, were increased when an intracellular signal was transferred by binding BMP and TGF-beta to the cell membrane receptors as described in the '867 publication (Detailed Description [0046]).

However, long before the '867 publication appeared, it has been known that Smad-1, Smad-2, Smad-3, Smad-5 and Smad-8 are R-Smads (regulatory Smads) bonded with receptors to transfer BMP/TGF-beta signal, and that Smad-4 was a co-Smad (common partner Smad) that bonded with R-Smad to promote a transfer signal to the cell nucleus. Furthermore, it has been known that Smad-6 and Smad-7 are I-Smad (inhibitory Smads) that inhibits transfer of BMP/TGF-beta to the cell by inhibiting function of R-Smad and co-Smad (Itoh. S. et al., Eur. J. Biochem., 267:6954, 2000; Miyazono K., J. Cell Sci., 113:1101, 2000). To sum up, the '867 publication insists that a series of the processes such as protein expressions and expression of BMP-2 and BMP-7 m RNA, secretion, receptor activation, Smads activation and bone formation and the like occur, if LMP, intracellular adaptor protein, is combined with PTD described in Detailed Description [0028] (Nagahara H. et al., Nature Med., 4:1449, 1998).

However, FIGS. 1-3 of the '867 publication showed that the expression of cellular BMP mRNA; Protein and bone matrix protein aggrecan was increased by the gene-transfer of adenovirus, not by the recombinant protein, and FIG 3~6 of the '867 publication showed the the LMP-1 gene overexpression by adenovirus results in an increase of bone formation in vivo. In other words, although the '867 publication describes that LMP-1, LMP-2 and LMP-3 recombined with PTD, it does not suggest intracellular delivery, intracellular processing and activation and extracellular secretion. Therefore, it did not provide scientific logic about an activation of LMP recombined

with PTD and a performance of intracellular function of LMP-PTD. Furthermore, the '867 publication applies the same theory to BMP and TGF-beta, extracellular proteins, and also applies the same theory to 1-Smad as well as all Smads that bind to BMP/TGF-beta receptor to transfer intracellular signal. Therefore, the '867 publication does not disclose anything from which the present invention is derivable.

In addition, based on experimental results, the present invention concretely suggests transfer of secreted protein BMP to cells, the processes of cleavage and activation by furin in cells and the secretion of activation protein. Unlike most intracellular proteins, secreted proteins such as BMP and TGF-beta have to accompany the following processes essentially in order to perform their function (Helenius A. & Aebi M., Annu. Rev. Biochem., 73:1019, 2004; Cabral c.M. et al., Trends Biochem. Sci., 26:619, 2001):

(1) transfer from intracellular endoplasmic reticulum (ER) to Golgi by prodomain and signal peptide as suggested in the description of the present invention;

(2) the activation by furin cleavage; and

(3) post-translational processing such as N-glycosylation of secreted protein.

In other words, although the '867 publication described TAT-BMP, it did not disclose a transfer of PTD-BMP to cells, a cleavage by furin and an active BMP secretion as required in the present invention. Therefore, the present invention cannot be easily conceived based on the '867 publication.

Based only on the '867 publication, it is difficult to predict the administration effect of the produced PTD-BMP. The example 1 of the present invention shows that hBMP of PTD-hBMP had activity only when it maintained 3-dimensional structure, suggesting that it still exhibits problems occurring in the art. In other words, the '867 publication does not disclose advantages of the present invention, solving problems caused by producing and storing while maintaining 3-dimensional structure, although the '867 publication describes PTD-BMP.

The idea that there is no need to maintain the 3-diminsional structure of hBMP in case of combining hBMP with both PTD and FAD while there are still the above-mentioned problems in case of combining hBMP with only PTD, is a novel approach when referring to the fact that the

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prior researches relating to BMP have concentrated on producing activated BMPs or introducing activated BMPs into cells with maintaining their activity. Therefore, the prior documents do not provide any motivation to form the subject matter of the present invention.

The examiner also states that a skilled artisan would be motivated to combine the elements because it was known in the art that absent the RX(K/R)R proprotein-cleavable domain the HIV-TAT/hBMP-2 construct would be cell-permeable but the resulting secreted protein would have no procollagen C-proteinase activity. However, it cannot be said that the present invention would have been motivated from Leighton, when considering the following two reasons:

1. The biosynthesized proteins in cells have their own secondary and tertiary structure by various molecular interactions such as specifically hydrogen bond and disulfide bond (Branden C. & Tooze J., Introduction to protein structure, 2nd Ed. 1999, Garland Publishing, USA). In addition, as stated by examiner, because the protein such as BMP has RX(K/R)R furin cleavage motif, the cleavage of prodomain and mature BMP consequently occur before mature BMP is secreted out of the cell. However, this intracellular processing demands the presupposition that the protein has its own secondary and tertiary structure, and Leighton's reference does not describe this fact. However, although the polypeptide of the present invention has the same amino acid sequences as described above, it has no secondary and tertiary structure because of the denaturing process by urea. Therefore, although the polypeptide of the present invention has RX (K/R)R furin cleavage motif, it cannot be said that the processing of Leighton's reference would naturally occur. That is to say, the processing as described in the Leighton's reference can be carried out only after all the processes such as transmission into cells, escape from lipid raft, exposure to water-soluble environment and restructuring of PTD-BMP, are successfully preceded. Therefore, it cannot be said that, without experimental basis, Leighton's reference provides any motivation to complete the present invention.

2. In addition, the present invention reflects the experimental basis that furin cleavage and activation of the BMP recombined with PTD of the present invention occurs although the recombinant (TAT-FAD-hBMP etc.) of the present invention has no signal peptide unlike BMP subjected to biosynthesis process in cells. Signal peptide plays a role of transferring the synthesized BMP in ribosome to endoplasmic reticulum (ER) and Golgi when BMP is

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biosynthesized in cells, and this process is essential for secreting the proteins having biological activity (Sakaguchi M., Curr. Opin. Biothecnol., 8:595, 1997). Actually, most of secreted proteins and cell-membrane proteins have signal peptides, and these signal peptides are essential for the activation of the proteins. However, according to experimental basis from the present invention, the BMP (ex. TAT-FAD-hBMP etc.) recombined with PTD of the present invention has the same effect as that of BMP having signal peptide although the recombinant has no signal peptide. This result suggests that the BMP (ex. TAT-FAD-hBMP etc.) recombined with PTD of the present invention involves different cellular processing from the BMP biosynthesized in cells. Therefore, it cannot be said that the present invention would have been motivated by the furin cleavage of Leighton's reference.

In addition, the present invention provides excellent economic effects in reducing the high cost of production, storage and/or administration processes of the conventional activated BMPs.

As shown by the foregoing, the combination of references cited by the examiner provides no derivative basis for applicants' claimed invention.

It therefore is requested that the rejection of claims be withdrawn.

D. Double Patenting Rejection

Claims 21 and 22 as previously pending were rejected on double-patenting grounds. Such claims have been cancelled in the present response, thereby obviating such rejection.

E. Fee Payable for Added Claims and Extension of Time

By the present Amendment, 2 new claims have been introduced, beyond the numbers for which payment was previously made. The fee of $50 for such added claims, and $60 for the one month extension of time for this response, for a total of $110, are paid by the enclosed Credit Card Payment Form PTO-2038.

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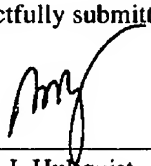
CONCLUSION

In light of the foregoing, all pending claims 1-2, 5-9 and 18-20, and 23-28 as amended/added herein, are fully patentably distinguished over the art and in form and condition for allowance. Favorable action is requested.

If any issues remain outstanding, incident to the formal analysis of this application, the examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss the resolution, in order that this application may be passed to issue at an early date.

Respectfully submitted,



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